Peer Review File

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Round 1: Response to the reviewer's comments:

Reviewer A:

This is very well written and an important topic. There are details missing about the methodology and data analysis that need to be included. I have provided the following recommendations to help strengthen this manuscript.

Methods

Comment 1:

Please provide some information about the goals/aims of the original/parent study, and sample size calculation. Was the present sub-analysis planned a priori? Or is this a secondary analysis of data.

Reply 1:

Thank you very much for your pointing this out. This study is the sub-analysis planned a priori. The original study was a prospective cohort study which aimed to develop a prognostic model to assist palliative care referral at least 3 months before death in

advanced cancer outpatients at medical oncology clinics (reference No.14). Sample size was not calculated statistically, it is a convenient sample according to patients' compliance of follow-up. We have added this description in the Methods.

Changes in the text:

p.9, lines 3 – 5 and lines 7 – 8.

Comment 2:

For data collection: where it states "enrolled patients were interviewed face to face", can you clarify what information was being collected during these interviews? The ESAS and EORTC QLQ are self-report questionnaires and typically filled out independently. Was other information collected during the interview?

Reply 2:

We appreciate your question. As you pointed out, ESAS and EORTC QLQ-C30 were self-administered, thus those were filled out independently by patients themselves. A research nurse met enrolled patients face-to-face to provide an outline of this study and obtained written consent from them. Therefore, as for this study, we did not use the data obtained from the interviews. We are sorry for the mistake. We deleted the description.

Changes in the text:

p.10, lines 5 – 6.

Comment 3:

Can you clarify what the operational definition of baseline and follow-up was.

Reply 3:

We appreciate your suggestion. Baseline was defined as the enrollment and follow-up was defined as the observation after approximate 3 months after enrollment. We have added the operational definition descriptions.

Changes in the text:

p.10, lines 15 - 16.

Comment 4:

There is no information about the time between the two assessments. This should be included in the methods and abstract. There is one sentence at the very end of the manuscript stating a three month assessment window – is this the time between assessments?

Reply 4:

Thank you very much for your advice. We agree with your suggestion. We assessed KPS,

K-ESAS and EORTC QLQ-C30 at enrollment and follow-up at an approximate 3-month interval. We have added this explanation.

Changes in the text:

p.5, lines 9 -10 and p.10 lines 15 – 16.

Comment 5:

At baseline, were these patients newly diagnosed with metastatic disease (de novo metastatic disease) or newly diagnosed with recurrence or incurable disease?

Reply 5:

Thank you for your question. We enrolled patients who had a diagnosis of advanced cancer (definition: metastatic or recurrent disease or progressive locally advanced disease not amenable to curative treatment) *before* the enrollment. Thus, patients were neither newly diagnosed with metastatic disease nor newly diagnosed with recurrence were at baseline As we described in Reply 6, all patients were enrolled after the diagnosis at advanced cancer.

Changes in the text:

N/A

Comment 6:

How long was the time between diagnosis and enrollment in the study (i.e. how long had these patients had cancer)

Reply 6:

Thank you very much for your question. We are sorry not to show the time between diagnosis and enrollment in the study because the data was not available. Instead, we have data the time between advanced cancer diagnosis and enrollment in the study. Thus, we have added the description about it in Table 1.

Changes in the text:

Table 1.

Statistical analysis

Comment 7:

How was missing data handled

Reply 7:

Thank you for your question. This study subjects were a subgroup completed longitudinal assessments from a parent study. In this subgroup, there was no missing data. Therefore, we did not mention about missing data.

Changes in the text:

N/A

Comment 8:

This study would be strengthened by evaluating other variables associated with symptom burden and survival such as a cox proportional hazards model. For example, 50% of the patients were on active chemotherapy treatment – what effect does this have on symptoms and overall survival? In addition, the majority of patients had lung cancer – a more symptomatic cancer with shorter survival. Without knowing the original aims of the study I am not sure if there would be statistical power to conduct this analysis.

Reply 8:

We appreciate your valuable advice. As we described in Reply 1, the original study aimed to develop a prognostic model to assist palliative care referral at least 3 months before death in outpatients with advanced cancer at medical oncology clinics. Thus, the relationship of symptom burden, chemotherapy and overall survival had been analyzed using a cox proportional hazards model in the published article (reference No.14) of the original study. The prevalence of primary cancer sites was almost same as

shown in the original study. However, as you pointed out, the heterogeneity of primary cancer sites might influence our results. We had described the heterogeneity in the section of limitation (p.17, lines 14 – 15).

Changes in the text:

N/A

Comment 9:

Was the a correction for multiple t-tests? Such as Bonferroni correction?

Reply 9:

Thank you for your question. We performed paired t-tests, those are not multiple t-tests. Therefore, the correction such as Bonferroni correction was not performed. This got confirmed from our statistician.

Changes in the text:

N/A

Discussion

Comment 10:

More details about methodology, as noted above, are important to include to provide

context for the discussion section. Without these details, the strength of the claims in the discussion are difficult to determine

Reply 10:

We appreciate your thoughtful comments. As we described in Reply 1 – 9, we have revised the method section accordingly.

Changes in the text:

N/A

Comment 11:

How does the information from this study fit with the larger goal of routine symptom monitoring of patient reported outcomes as a standard of care. This is becoming the norm in many cancer organizations world wide. If routine symptom monitoring is already occurring, what does this study add?

Reply 11:

Thank you very much for your questions. We agree that routine symptom monitoring of patient reported outcomes -such as ESAS and EORTC QLQ-C30- is becoming the norm in many cancer organizations worldwide. However, few studies have reported the association between longitudinal assessment of patient reported outcomes and survival

time (p.8 lines 8 - 10). Thus we proved the usefulness of changes from longitudinal symptom assessment of patient reported outcomes as a novel prognostic information (p14. lines 3 - 8).

Changes in the text:

N/A

Limitation

Comment 12:

A major limitation of this study is small sample.

Reply 12:

Thank you very much for pointing this out. We totally agree with your suggestion. We have added the description in the section of limitation.

Changes in the text:

p.18, lines 1 – 3.

Comment 13:

If information about how long patients had metastatic disease is not available, this is also a major limitation of the study

Reply 13:

Thank you for your advice. As in Reply 6, the data was available for the time between advanced cancer diagnosis enrollment in the study. We have added the data in Table 1.

Changes in the text:

Table 1

Comment 14:

The characteristics of the participants (majority with lung cancer and 50% on treatment) and the possible effect this may have on the results needs to be addressed in the limitations.

Reply 14:

We appreciate your suggestion. We agree with your view. We have addressed the characteristics of the participants and the possible effect in the section of limitation.

Changes in the text:

p.17, lines 10 – 12.

Comment 15:

Although some findings are statistically significant, there are very wide confidence intervals. What does this mean with respect to the conclusions you have drawn about the results?

Reply 15:

Thank you very much for your question. In this study, inclusion criteria was less than a year of clinician's prediction of survival (CPS). However, CPS is well-known to be overly optimistic through previous studies. As a result, the median survival time of the participants ranged from 118 days to 1103 days in our study. Another factor is sample size. Since our study subjects were small, it would increase confidence interval, too. We recognize, the wide confidence intervals may indicate the strength of our results can vary according to clinical settings. However, the significance (p values) of our results would not change according to wide confidence intervals. Thus we regard our conclusions remain the same. We believe this was one of the limitations from small sample size.

Changes in the text:

N/A

Table 1

Comment 16:

Median follow-up duration is 92 days. Is this the time between baseline and follow-up assessment? Indicating that follow-up assessment was not set to a specific time?

Reply 16:

Thank you very much for your questions. The median follow-up duration means the time from baseline till follow-up assessments. The follow-up assessment was set to an approximate 3-month interval. We have added the explanation in the section of Methods.

Changes in the text:

p.10, lines 15 – 16.

Table 2

Comment 17:

Please include the follow-up time (e.g. 90 days)

Reply 17:

We appreciate your suggestion. We have added the information in Table 2.

Changes in the text:

N/A

Comment 18:

Please include a brief description of how KPS, ESAS and EORTC are scored. For example ESAS is scored on a scale of 0-10 with higher scores indicating more severe symptoms.

Reply 18:

Thank you for your valuable advice. We have added brief descriptions for KPS, ESAS and EORTC QLQ-C30 scoring as footnotes in Table 2.

Changes in the text:

Table 2

Reviewer B:

I found this interesting manuscript to be comprehensive with respect to rationale and methods. Understanding the influence of changes in symptomatology on the survival time of patients with advanced cancer may lead clinicians to provide better palliative care interventions. Most of the available evidence on the survival time and prognosis of cancer patients is related to the symptom assessment at the start of palliative care and not over time, therefore, studies covering other approaches as changes in symptoms over time is a contribution to global knowledge in palliative care.

There are few important comments I would like to add:

Comment 1:

Methods (participants, page 4): The patients included in this study were collected from a preliminary cohort study from the same cancer center (reference #17), but this is not highlighted in the methods section as necessary, only is mentioned in summary. Additionally, in the results you wrote “the parent study enrolled a total of 200 patients from March 2016 to January 2019. Its details are described in elsewhere ….” . This can be simplified explaining that from 200 patients completing the baseline assessment, only 60 completed the follow-up part, for example. Because this is a secondary study you can provide this information in the methods section and then describe study population in the results. This may guide readers to better follow the inclusion of patients in this study.

Reply 1:

We appreciate your valuable advice. We have clarified that this study was a subgroup analysis of a prospective cohort study which aimed to develop a prognostic model to assist palliative care referral at least 3 months before death in outpatients with advanced cancer at medical oncology clinics in Methods. In fact, as Reply 1 to Reviewer A, this is not a secondary analysis. This is pre-planned subgroup study. However, the participants were convenient sample due to compliance matter of follow-up. In Results, we added the description about participant selection accordingly.

Changes in the text

p.9, lines 3 – 5 and p.12, lines 7– 9.

Comment 2:

Methods (participants, page 4): As I can read from the cohort study, where same authors participated, patients completed the KPS and ECOG at the start of the study, but the EORTC QLQ-C30 and ESAS are not mentioned in any part of the previous paper. Were all these 4 instruments part of the cohort protocol (baseline and follow-up assessments? How did you choose relevant patients for secondary analyses? Please provide more information in this section.

Reply 2:

Thank you very much for your comments. The instruments (KPS, ECOG-PS, K-ESAS and EORTC QLQ-C30) were part of the parent prospective cohort study's protocol. The participants for this study were the patients who completed longitudinal assessments. Therefore, participants for this study were chosen conveniently as we mentioned above Reply 1. We have added the explanations in the section of Methods.

Changes in the text:

p.9, lines 7 – 8 and p.10, lines 5 – 6.

Comment 3:

Methods (Data collection, page 4): The reference No.10 does not correspond to the EORTC QLQ-C30 scoring manual, Fayers et al. in 2001 developed the manual.

Reply 3:

We appreciate your pointing this out. We apologize for the unmatched reference. As you suggested, we should cite Fayers's paper for EORTC QLQ-C30 scoring manual. We have modified the reference list accordingly.

Changes in the text

p.10, line 15

Comment 4:

Methods (Data collection, page 4): What is the evidence you found to decide that at least 1 one level of improvement/worsening in the scales of the KPS/ESAS/EORTC QLQ-C30 was adequate to define the patient groups for analyses ("Improved + Stable" and "worsened"), especially for the EORTC QLQ-C30 questionnaire. According to your manuscript, based on references No. 12 and 16 you decided the division of patients' groups, but one study included the ESAS and the other IPOS. Several clinical trials have

shown that Minimal clinically important differences (MCIDs) are clinically relevant when there is a change in at least 2-4 units of any EORTC QLQ-C30 symptom/scale (improvement or worsening). It would be important to justify and defend with evidence in the methods and discussion section why you have chosen same cutoff-point for all instruments.

Reply 4:

We appreciate your comments. We have added the definition of improvement or worsening scale in the section of Methods. Regarding MCIDs for EORTC QLQ-C30 score, we checked the scoring manual. The manual described that "Patients who reported 'a little' change for better or worse on a particular scale (function or symptom) had QLQ-C30 changes about 5 to 10. Those reporting 'moderate' change had changed about 10 to 20, and 'very much' change corresponded to a change greater than 20." According to this description, we defined a change of 10 points as a one level change based on a previous study (reference No.19). The results for summary score changed according to revised definition, therefore, we have modified Table 3.

Changes in the text:

p.11, lines 8 – 9 and Table 3.

Comment 5:

Results (Survival by changes in symptoms, page 5-6): In this part of the results you presented the statistically significant and not significant results for KPS, ESAS and EORTC QLQ-C30. It would be helpful for the readers to understand these multiple results, only include significant results for all instruments, since all the rest of the information is provided in table 3.

Reply 5:

Thank you very much for your suggestion. We have modified to show only significant results for all instruments accordingly.

Changes in the text:

p.13, lines 8 – 11.

Comment 6:

Discussion (page 7): You wrote “To the best of our knowledge, this is the first study to investigate the influence of changes in symptoms and QOL on survival time in ambulatory patients with advanced cancer who have more than several months of median survival…”. What is more than several months? a very broad sentence that makes no sense if you don't include numbers that you already have in your results.

Reply 6:

We appreciate your pointing this out. We do agree with your view. We specified the sentence as “more than three months of survival time” based on the participants’ survival time (range: 118 – 1103 days).

Changes in the text:

p.16, line 14.

Comment 7:

Discussion (page 7): You wrote “Evidence from several patient-reported outcomes studies suggest that symptoms are generally under-recognized by oncologists, in both incidence and severity…” which are the studies that suggested this?, where are the references ?.

Reply 7:

Thank you very much for your comments. As you pointed out, the references are needed. Therefore, we have added the references (reference No. 32 and 33).

Changes in the text:

p.17, line 3.

Reviewer C:

The introduction is well written with clear and justified aim and hypothesis.

Methods

Comment 1:

The type of study design needs to be mentioned.

Reply 1:

Thank you for your advice. We have added the explanation for the type of study design in the section of Methods.

Changes in the text:

p.9, lines 3 – 5.

Comment 2:

A more thorough description of the study design is warranted. E.g. time to follow-up and number of follow-ups are not mentioned until late in the Discussion Section of the manuscript.

Reply 2:

We appreciate your pointing this out. We have added the description about participants selection and follow-up in the section of Methods accordingly.

Changes in the text:

p.9, lines 7 – 8 and p.10, lines 15 – 16.

Comment 3:

The chosen univariate analysis model is quite simplistic and does not adjust for potentially confounding factors. Also, I am not entirely sure what the authors mean by “one level of worsening in the scale” and how this correlates with the official EORTC Scoring Manual where a change of 10 points is generally considered clinically meaningful. Could the authors please elaborate and/ or justify the chosen model?

Reply 3:

We appreciate your valuable advice. In this study, we had chosen the univariate analysis for simple and intuitive clinical implication (Suh SY, Won SH, Hiratsuka Y, et al. Assessment of Changes in Symptoms Is Feasible and Prognostic in the Last Weeks of Life: An International Multicenter Cohort Study. J Palliat Med. 2021; Epub ahead of print.). According to your advice, we have clarified the definition that a change of 10 points for EORTC QLQ-C30 was a one level change, based on a previous study (reference No.19).

Changes in the text:

p.11, lines 8 – 9.

Response to the editorial comments:

1. Please follow the attached “Submission Checklist for Authors” and revise your paper if needed. Here are some additional points:

Comment 1:

a. The article already followed a Checklist for reporting standards. Please place “Y” in the “Submission Checklist”.

Reply 1:

Thank you for your comments. We have modified the manuscript according to the checklist.

Changes in the text:

p.6, line 8 and p.8, lines 17 – 18.

Comment 2:

b. “Data Sharing Statement” is a statement made by authors to confirm their willingness of sharing raw data/patient information related to the article with others. We attached a

template for your reference.

Reply 2:

Thank you for your comments. We have made “Data Sharing Statement” referring to the attached template.

Changes in the text:

N/A

Comment 3:

c. Conflict of Interest (COI) Form must be provided, as suggested by ICMJE: (http://www.icmje.org/conflicts-of-interest/). Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. COI form download link: https://cdn.amegroups.cn/static/public/coi_disclosure.docx.

Please collect all forms from each author, number all forms in the line-up of authorship and submit them to the editorial office. We also attached two templates for your reference.

Reply 3:

Thank you for your comments. Although we provided COI Form (ICMJE) at first submission, we provided them again. Please confirm them.

Changes in the text:

N/A

Comment 4:

d. Please indicate if any of the authors is serving as a current Editorial Team member (such as Editors-in-Chief, Editorial Board Member, Section Editor) for this journal.

Reply 4:

Thank you for your comments. No author serves as a current Editorial Team member (Editorial Board Member).

Changes in the text:

N/A

Comment 5:

e. Please confirm that all figures/tables/videos in this manuscript are original; if not, permission is needed from the copyright holder for the reproduction.

Reply 5:

Thank you for your comments. We have confirmed the originality.

Changes in the text:

N/A

Comment 6:

f. We are using the “Submission Checklist for Authors” to double-check your manuscript, place “Y” on blank space if you confirm your manuscript has followed the requirement. Place “N/A” if not applicable. If further explanation is needed on a certain item, you can copy the Item and write explanations down below. A filled “Submission Checklist for Authors” should be submitted to the editorial office, along with other required documents.

Reply 6:

Thank you for your comments. We have confirmed our manuscripts according to the “Submission Checklist for Authors”.

Changes in the text:

N/A

Closing comments to the editor：

We do appreciate that you gave us the opportunity to revise our work for consideration for publication in *Annals of Palliative Medicine.* We hope our revised manuscript meets your standards.

Round 2: Response to the reviewer

Thanks for the responses to our comments and the changes you made to improve your manuscript. There are still two topics pointed out in the review but that you not fully covered.

Comment 1:

There is not a clear description on the scoring of the instruments included in this study, for example the EORTC scores are transformed into 0-100 points scale. There is not as footnote in table 2 including this information or in any other part of the manuscript as you mentioned in your letter. Please include the scoring of the EORTC, ESAS and KPS.

Reply 1:

Thank you very much for your pointing this out. We had revised the tables previously but somehow they were not reflected in the revised manuscript (APM-22-33-R1). We are not sure what happened. To further address this issue in the current revision, we've also added description of these important measurement/scoring issues in the Methods section and as a footnote in Table 2.

Changes in the text:

p.10, lines 2 – 6 and Table 2.

Comment 2:

Because previous information is missing it is difficult to understand how did you classify the subgroups for the analysis (improved, stable, worsened). Also the change you made from selecting 1 point difference in the EORTC scores to 10 points difference as final cut-point for subgroup classification is not clearly justified as requested.

Reply 2:

Thank you very much for your advice. Previously, we selected a “1 level” difference in the EORTC scores. It was therefore actually not a “1 point difference,” since one level in EORTC scoring ranged from approximately 8 to 13 points, depending on the particular domain in question. Thus, we utilized a unified cut-point of 10 points, based on a prior publication, which we have now added as a reference in the revision process.

Changes in the text:

p.10, lines 12 – 13.